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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,351	11/16/2000	Ari Ayalon	1662/50302	6513

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EXAMINER	
STOCKTON, LAURA LYNNE	
ART UNIT	**PAPER NUMBER**
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/714,351	AYALON ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7-15,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending in the application.

Response to Amendment

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. The indicated allowability of claim 2 is withdrawn.

Applicant's arguments with respect to claims 1, 3-6, 16 and 17 have been considered but are moot in view of the new ground(s) of rejection.

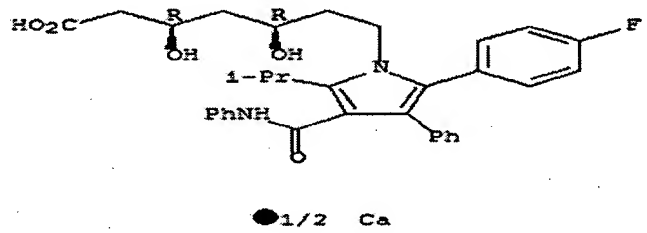
Election/Restrictions

Applicant's election without traverse of Group I (claims 1-6, 16 and 17 - drawn to Atorvastatin calcium Form V product) in the response filed February 24, 2004 was acknowledged in a previous Office Action. As noted

below in the STN record, Atorvastatin calcium is known by many names, such as Atorvastatin hemicalcium and Lipitor. The requirement was deemed proper and made FINAL in a previous Office Action.

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 134523-03-8 REGISTRY
ED Entered STN: 28 Jun 1991
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), (βR,δR)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), [R-(R*,R*)]-
OTHER NAMES:
CN Atorvastatin calcium
CN Atorvastatin hemicalcium
CN Atorvastatin hemicalcium salt
CN CI 981
CN Lipitor
CN Sortis
CN Tahor
CN YM 548
FS STEREOSEARCH
DR 334757-04-9
MF C33 H35 F N2 O5 . 1/2 Ca
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HSDB*, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (134523-00-5)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

370 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
374 REFERENCES IN FILE CAPLUS (1907 TO DATE)

Claims 7-15, 18 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in the response filed February 24, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

The nature of the invention is Atorvastatin calcium Form V. The state of the prior art is that the most useful method to compare X-ray powder diffraction data is to overlay and align the respective films or plots. The ensuing comparisons of peak positions and intensities will show whether the structures are the same or different (Byrn et al., Solid-State Chemistry of Drugs (1999), SSCI, Inc., Indiana, pages 62-63 especially page 63). An x-ray diffraction pattern is like a "fingerprint" and Applicant has not provided why the certain peaks found in the claims are the only required peaks in the x-ray diffraction pattern or the signals in the ^{13}C NMR that must match.

The peaks present in the claims 3 and 17 and the ^{13}C NMR signals in claims 5 and 17 do not include all peaks of the x-ray diffraction pattern or all the signals in the ^{13}C NMR, nor does the specification provide any

direction or guidance as to why certain peaks and signals are the only required peaks and signals in the x-ray data or the ^{13}C NMR. Claims 3, 5 and 17 are only drawn to certain peaks and signals which is not the entire "fingerprint". The amount of direction present in the specification is the x-ray diffraction and the ^{13}C NMR of Atorvastatin calcium Form V. Figures 1 and 2, and page 6 disclose the data for Atorvastatin calcium Form V. Applicant has not provided why the entire "fingerprint" is not being claimed, nor does Applicant provide why only certain peaks and signals are found in the claims and not others. The claims to only certain peaks and certain signals do not find written description in the specification as the claims do not include the entire "fingerprint" and the specification fails to provide any description as to why the data claimed is characteristic of Atorvastatin calcium Form V and why the entire "fingerprint" is not required. Therefore the claims are rejected as there is

no written description as to why the data present is the only data required from the "fingerprints" to distinguish Atorvastatin calcium Form V from other forms. In terms of the specific X-ray peaks and ^{13}C NMR signals found in the instant claims, the specification should have disclosed: (1) how the peaks or signals were selected; (2) if the peaks or signals are subject to preferred orientation effects; (3) if all of the peaks specific in the presence of excipients (see instant claim 16); and (4) if there are any perturbations after formulation.

Additionally, claims 1-6, 16 and 17 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims are drawn to Atorvastatin calcium Form V with certain X- ray and ^{13}C NMR data. However, the specification disclose in

Figures 1 and 2, and on page 6 that the data provided in the instant claims is for Atorvastatin calcium Form V. There is no written description in the originally filed disclosure for hydrates of Atorvastatin calcium Form V with the claimed X-ray and ^{13}C NMR data. Therefore, the claims lack written description as such.

Claims 1-6, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Atorvastatin calcium Form V which has an X-ray powder diffractogram as found in Figure 1 and a solid state ^{13}C NMR spectrum as found in Figure 2, does not reasonably provide enablement for any hydrate of Atorvastatin calcium Form V nor a pharmaceutical composition comprising a therapeutic amount of Atorvastatin calcium Form V. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

Applicant is claiming hydrates of Atorvastatin calcium Form V. On page 7, lines 1-4 of the instant specification, Applicant states "the Atorvastatin calcium Form V can be in various states of hydration,

between 0 and 9 moles of water." Therefore, the instant claims are read as claiming multiple crystalline forms of Atorvastatin calcium.

Claims 3 and 5 are claiming multiple crystalline forms of Atorvastatin calcium products as can be seen by claims 3 and 5 which state that the products are characterized by (open language) X-ray powder diffraction peaks and ^{13}C NMR signals that do not have to be those disclosed in instant Figures 1 and 2. Therefore, the claims are directed to multiple crystalline forms.

Furthermore, the hydrates of Atorvastatin Calcium as claimed would also have different X-ray diffraction patterns than Atorvastatin calcium, which therefore renders the claims as claiming multiple products with varying X-ray diffraction patterns.

Applicant is also claiming a pharmaceutical composition comprising a therapeutic amount of Atorvastatin calcium Form V (see instant claim 16).

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that polymorphism is the existence of different solid forms (modifications) of a compound, which have the same chemical composition but different structures and thus different physical and sometimes also chemical properties (see Concise Encyclopedia Chemistry (1993), Walter de Gruyter Berlin-New York, pages 872-873). Polymorphs (compounds that are characterized by substantially the X-ray pattern in Figure 1, or containing only one characteristic of Form V or having the same chemical shift differences) of Atorvastatin Calcium with the claimed X-ray diffraction patterns would include other forms without the claimed specific X-ray diffraction patterns since polymorphs are different forms.

It is the state of the prior art that under any given pressure and temperature, other than the conversion points, only one modification is stable, the

one with the lowest vapor pressure. Often, the conversion rate in the solid phases is so slow that even modifications, which are unstable under the conditions, can be kept for a long time in their metastable state. This conversion rate can depend on the rate of temperature change or pressure change (Concise Encyclopedia Chemistry, 1993). The predictability or lack thereof in the art is that there can be multiple forms of a solid in existence and these polymorphs are created by varying crystallization processes which began with varying starting materials, utilize varying solvents, varying temperatures and varying reaction times. There is no method that exists to predict the polymorphs of a solid compound with significant certainty (Rouhi, Chemical and Engineering News, February 24, 2003, pages 32-35, especially page 32). Furthermore, in addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of

the crystal structure. Just as every polymorph has its one characteristic X-ray diffraction pattern, so does every solvate (US Pharmacopia #23, National Formulary #18 (1995), pages 1843-1844, especially page 1843). Additionally, sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached (US Pharmacopia, page 1843).

The state of the prior art is that the preparation of pharmaceutical compositions requires creating solutions, milling, adding diluents, excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the metastable state to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32). The state of the prior art that an

acceptable carrier for a pharmaceutical formulation can be water, which embraces a suspension. Dissolving a specific crystalline form in water, creating an aqueous solution, would put the compound in its free form and not in a crystalline form with a specific X-ray diffraction pattern. The use of a wrong polymorph of a drug when using an aqueous vehicle may provide a phase conversion from the metastable to stable polymorph (Haleblian et al., Journal of Pharmaceutical Sciences, August 1969, Volume 58, No. 8, pages 911-929, especially page 912).

The predictability or lack thereof in the art concerning a pharmaceutical composition, as found in instant claim 16, is that a metastable compound will resort back into its most thermodynamically stable form which would have a different X-ray diffraction pattern and also that a solution prepared from a specific crystalline form and water would contain the free form of the compound.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present for the elected invention is for the specific compound, Form V, of Atorvastatin Calcium that has the X-ray diffraction pattern of Figure 1 and the solid state ^{13}C NMR of Figure 2.

The instant specification does not disclose the X-ray diffraction patterns or the solid state ^{13}C NMR of any hydrate form of Atorvastatin calcium Form V. The specification provides no guidance as to the maintenance of the X-ray diffraction in a pharmaceutical formulation.

With regards to the pharmaceutical composition, while the specification has provided processes for the preparation of Atorvastatin calcium Form V and generic processes for preparing pharmaceutical compositions (pages 11-13 of the instant specification), the specification fails to provide the steps of ensuring

that the pharmaceutical compositions will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound.

The quantity of experimentation needed

The quantity of experimentation is extremely high. One would need to prepare crystalline compounds of Atorvastatin calcium by many different methods to obtain any polymorph of Atorvastatin Calcium while the specification only provides methods and direction to the elected invention with the X-ray diffraction pattern of Figure 1 and the solid state 13 C NMR of Figure 2. Further, the quantity of experimentation needed is undue as it pertains to the pharmaceutical composition of instant claim 16. One of ordinary skill in the art, without direction, would be unable to maintain a specific metastable crystalline form upon

preparation into a pharmaceutical composition, which may require milling or the formation of a solution.

The level of the skill in the art

The level of skill in the polymorph art is high. However, without a showing or guidance as to how to make other polymorphs, besides the Form V as elected and described in the specification, it would require undue experimentation for one skilled in the art to figure out what starting materials, solvents, temperatures and reaction times would provide other polymorphs of Atorvastatin calcium.

Additionally, it is well recognized by an artisan having ordinary skill in the field that X-ray diffraction (such as claimed in instant claims 2, 3 and 17) while being able to show crystallinity does not provide chemical identity information. Seddon {Crystal Growth & Design, 4(6), (2004), pages 1087} disclose that for a chemical product, there is no good reason

why the product identity cannot be obtained to non-ambiguously identify a chemical product. Pseudopolymorphs (i.e., hydrates) should have no difficulty in this century to be identified by its chemical identity. While powdered X-ray diffraction (PXRD) can be useful in delineating crystalline structure, it does not offer reliable information on chemical identity of a material. It is well recognized in the art that powdered X-ray diffraction can be drastically different from its single crystal X-ray (see Bernstein, "Polymorphism in Molecular Crystals", Clarendon Press, Oxford (2002), pages 117, 118 and 272, see especially page 118) and identical powdered X-ray diffraction would be obtained for different chemical material were the crystalline structures identical (see Bernstein page 272).

Davidovich et al. {American Pharmaceutical Review, 7(1), (2004), pages 10, 12, 14, 16 and 100} clearly teach that X-ray diffraction pattern, especially

powdered X-ray diffraction pattern includes many artifacts, thus, just because there are some difference, without other confirmation, different X-ray alone is no proof of a new polymorph. This very same principle has also been disclosed in the reference, the US pharmacopia, where it states that many crystalline products showed small differences in X-ray diffraction pattern and whether difference is a true polymorph must be evaluated.

While the level of skill in the art is high, one of skill in the art would be unable to maintain a specific metastable crystalline form upon the preparation of a pharmaceutical composition without direction and guidance, which is not found in the instant specification. One of skill in the art would expect the pharmaceutical composition to contain the free form of the compound or the most thermodynamically stable form of the compound.

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art and lack of guidance and direction, one skilled in the art could not use the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 16 and 17 are indefinite because hydrates of the solid crystalline Atorvastatin calcium would also have different X-ray diffraction patterns

than solid crystalline Atorvastatin, and therefore renders the claims indefinite as claiming multiple products with non-varying X-ray diffraction patterns and ^{13}C NMR spectra.

Claims 1-6, 16 and 17 are indefinite because of the expression "or hydrate thereof" since a hydrate of Atorvastatin calcium would not be Form V.

The meaning of "substantially" in claims 2 and 4 is unclear since claims 2 and 4 are directed to the specific X-ray powder diffractogram of Atorvastatin calcium Form V and the solid state ^{13}C NMR spectrum of Atorvastatin calcium Form V, respectively. Therefore, claims 2 and 4 are indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by:

a) Mills et al. {U.S. Pat. 5,686,104} - see Example 4 in columns 8-10;

b) Briggs et al. {WO 97/03959} - see Example 1 on page 26 and pages 24-26; or

c) Roth et al. {U.S. Pat. 5,273,995} - see Example 10 in columns 14-16.

Each of the above cited prior art disclose products which are embraced by the instant claimed invention. Therefore, each of the above cited prior art anticipates the instant claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the

examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

August 2, 2007